UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,163	02/28/2007	Guido Bold	33381-US-PCT	6615

1095 7590 01/05/2010

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	**PAPER NUMBER**
1628	

MAIL DATE	DELIVERY MODE
01/05/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,163	BOLD ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-22* is/are rejected.

7)☒ Claim(s) *22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicants' arguments, filed 10/23/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. Applicant's arguments with respect to the rejection under 35 USC 112, 2nd paragraph have been fully considered but they are not fully persuasive:

Claims 20 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The application of this rejection to the new claims is necessitated by the claim amendment.

The abbreviation “VEGF”, without the meaning (Vascular Endothelial Growth Factor?) accompanying the abbreviation at the first occurrence in the claims, does not make clear that the meaning recited in the specification controls the meaning of the abbreviation in the claims.

Applicant argues the new claims overcome the reasons that the claims were rejected under 35 USC 112, 2nd paragraph. This is persuasive for all the reasons except that discussed above; i.e., the abbreviation "VEGF" is still present in the claims

without being accompanied by the meaning at the first occurrence, rendering the scope of the instant claims indefinite.

3. Applicant's arguments with respect to the rejection under 35 USC 103 have been fully considered but they are not persuasive:

Claims 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wood et al. ("PTK787/ZK 222584, a Novel and Potent Inhibitor of Vascular Endothelial Growth Factor Receptor Tyrosine Kinases, Impairs Vascular Endothelial Growth Factor-induced Responses and Tumor Growth after Oral Administration"; 2000; Cancer Research; 60: 2178-2189; cited in a prior Office Action) and Remiszewski et al. (US 6,552,065 B2; 2003 Apr; filed 2001; priority 2000; cited in a prior Office Action).

The application of this rejection to the new claims is necessitated by the claim amendment. The rejection is maintained for the reasons of record, which are applicable to the new claims, and for the reasons that follow.

Applicant argues that the article Qian et al. ("The Histone Deacetylase Inhibitor NVP-LAQ824 Inhibits Angiogenesis and Has a Greater Antitumor Effect in Combination with the Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor PTK787/ZK222584"; 2004, 15 Sept; Cancer Research; 64:6626-6634; provided by applicant in the 10/23/2009 Reply) is not prior art, because of the claim of priority to Provisional Application No. 60/505250, filed 9/23/2003. Qian describes experiments wherein the combination of a VEGF inhibitor, PTK787, and a histone deacetylase inhibitor, LAQ824, show a greater in vivo antitumor effect compared with single agents

and a synergistic effect in isobologram A on p. 6630; that the experiments described in Qian demonstrate the patentability of the presently claimed invention.

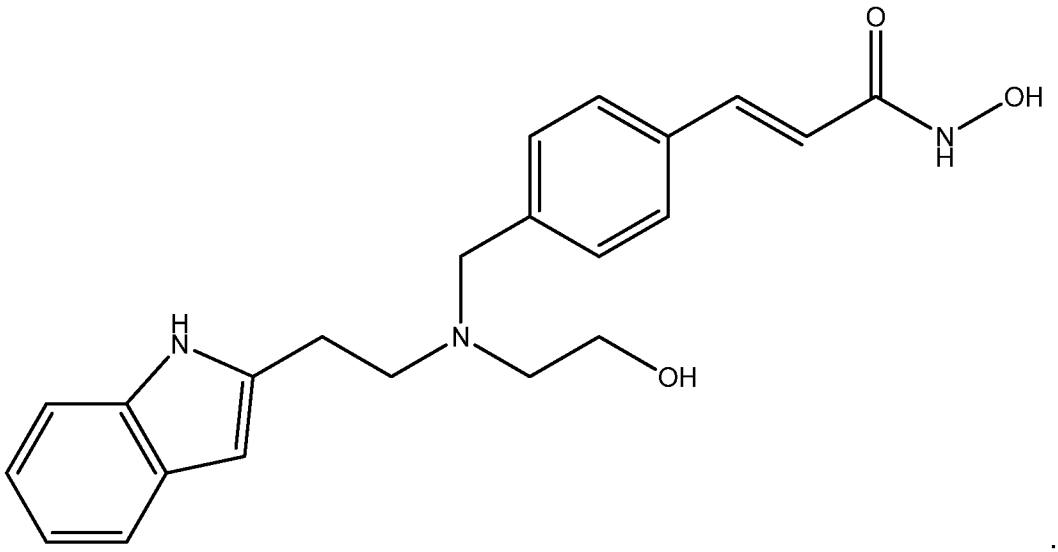
A review of the teachings of Qian indicate that there is demonstrated synergism for three specific combinations of the two compound PTK787 (the elected VEGF inhibitor compound) and NVP-LAQ824 (a non-elected histone deacetylase inhibitor compound). These are depicted in Figure 3. As indicated in Fig 3 A, the range for which synergy was observed is the range of concentrations from 50-250 nM LAQ824 and 100-500 nM PTK787, which is significantly narrower than claims to any amount of each compound. Additionally, B and C of the figure indicate the ED_{25} (about 50nM LAQ824 and 100nM PTK787 has a combination index of 1, corresponding to additive behavior, and only amounts corresponding to the ED_{50} to ED_{75} range are synergistic. This result is characterized by Qian as "additive or slightly synergistic effect" (p. 6629, 2nd paragraph, near end).

Additive behavior is predicted based on an *In re Kerkhoven* type combination of two compounds, especially for compounds with different mechanisms of action. Therefore, only a limited range of concentrations from about 150-250 nM LAQ824 and 300-500 nM PTK787 corresponds to a result that is unexpected over the combination based on the references the rejection is based on. None of the instant claims recite these amounts or ranges similar to these amounts. Therefore, the instant claims are not commensurate in scope with these amounts.

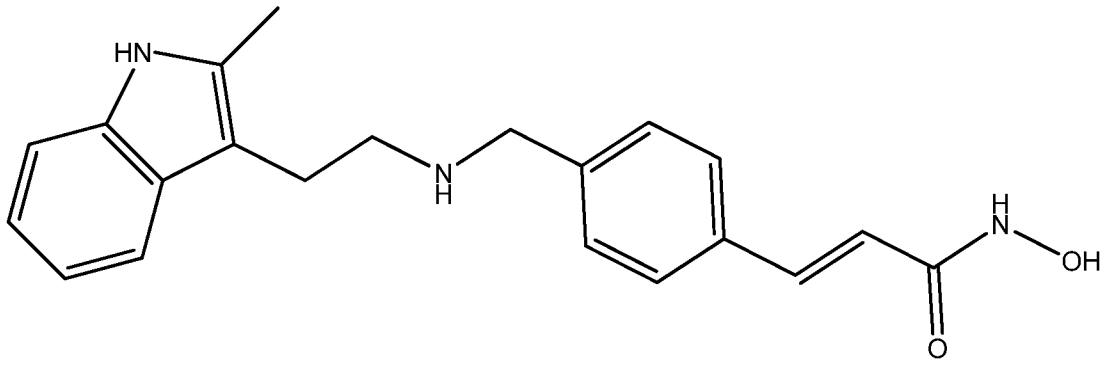
With respect to the in vivo data, Qian observed that the combination was more effective than single agents alone, single agents provided blood vessel formation of

about 50% inhibition, compared to the drug combination at about 60% inhibition (p. 6629, 3rd paragraph; Figure 5). This is not a synergistic effect, and is not taken as unexpected over the references of record. However, even if a persuasive argument were presented that this result is somehow unexpected, the result is still limited to a single specific dose of each compound administered, which is not commensurate in scope with any of the instant claims.

Finally, the compound used by Qian as the histone deacetylase inhibitor, LAQ 824, has the structure:



This compound is the last named compound of claim 22, but is not the elected compound under examination, LBH 589, which has the structure:



While these compounds are structurally similar and have the same mechanism of action as histone deacetylase inhibitors, the unexpected synergy observed for a combination involving one of these compounds would not necessarily be extended to a combination involving a structurally distinct compound; i.e., the unexpected results of Qian, for a non-elected compound combination, are not necessarily predictable for the different combination of compounds under examination. None of the instant claims is even limited to the two compounds studied by Qian, or to the elected combination of compounds.

The unexpected results for the combination taught by Qian at the amounts for which synergism is taught are not sufficient to overcome the much broader claims under examination, including the elected compound species subject matter basis under examination, on which the rejection is based. Therefore, the rejection is maintained.

Claim Objections

4. Claim 22 is objected to because of the following informalities: the 2nd named compound of the claim has an improperly mismatched number of parentheses in the compound name. Appropriate correction is required.

Specification

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Combination of a VEGF Receptor Inhibitor and a Histone Deacetylase Inhibitor.

Conclusion

6. No claim is allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is

(571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1628

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642